5626/tat "PATENT APPLICATION"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

GARY LOCK ET AL

U.S. Serial No. 10/031,364 Group Art Unit 1753

Filed: February 19, 2002 A. Diamond, Examiner

TRAVELING WAVE DIELECTROPHORETIC APPARATUS AND METHOD

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Alexandria, Virginia
January 18, 2008

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

RESPONSE TO NOTIFICATION OF NON-COMPLIANT APPEAL BRIEF

Dear Sir:

A Notification of Non-Compliant Appeal Brief mailed January 4, 2008 states that the Appeal Brief filed March 12, 2007 does not contain a statement of the status of all claims on appeal. Applicants are submitting herewith an amended appeal brief in response to the Notification. The defect as noted in the Notification has been corrected as follows:

The language "Claim 26 has been canceled" has been added under the subheading "Status of Claims".

Accordingly, applicants have addressed the matter set forth in the Notification mailed January 4, 2008. Favorable consideration of the appeal is requested.

Respectfully submitted,

GARY LOCK ET AL

By 

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BRIEF ON APPEAL

Dear Sir:

This appeal is from the action of the Primary Examiner mailed July 12, 2006 rejecting claims 1-25 and 27-31.

Appellants' brief fee of $250 was previously submitted March 12, 2007. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-3690 of the undersigned attorney.

Real Party in Interest

The named inventors of the captioned application have assigned their entire rights to University of Wales, Bangor, Gwynedd, Great Britain.

Related Appeals and Interferences

No appeal or interference is known to appellants which will directly affect or be directly affected by or have a bearing on the Board's decision in this pending appeal.

Status of Claims

The claims pending in this application are claims 1-25 and 27-31 as set forth in the Appendix hereto. Claims 1, 16, 23 and 27 are the only independent claims. Claim 26 has been canceled. All pending claims are currently rejected.

Status of Amendments

No response was made to the final official action mailed July 12, 2006.

Summary of Claimed Subject Matter

Independent claims 1, 16, 23 and 27 are described below with reference to the specification.

Independent claim 1 (as described at page 4, lines 1-10) claims a method for determining properties of a particle, including response of the particle to exposure to a chemical or physical agent, and for separating particles

of more than one type, comprising steps of applying to a suspension of particles in a stationary fluid a first signal at a first frequency and at a plurality of different phases whereby the particles experience a traveling wave dielectrophoretic force of which there is a real part which is negative and of which there is also an imaginary part, and simultaneously applying a second signal at a second frequency whereby either the real part or the imaginary part of the traveling wave dielectrophoretic force on the particles at the first frequency is altered in magnitude.

Independent claim 16 (as described at page 4, lines 12-28) claims a method of separating unwanted particles from body fluid particles comprising applying to a suspension of both types of particles in a stationary liquid a TWD field at a first frequency, and simultaneously applying a second electrical field at a second frequency, whereby speed or direction of travel in the TWD field of one particle type is altered.

Independent claim 23 (as described at page 15, line 6 to page 17, line 1, and shown in Figure 9) claims an apparatus for applying traveling wave dielectrophoresis comprising a dielectrophoresis cell (page 15, lines 7 and 19-22; Figure 9, 20) for receiving a fixed quantity of a

stationary suspension of particles in a liquid, an electrode array (page 15, lines 7-8; Figure 9, 22) on a substrate forming a wall of the cell, first frequency signal generating means (page 15, lines 9 and 22-29; Figure 9, 26) to provide a traveling wave dielectrophoretic force, second frequency signal generating means (page 16, lines 10-16) to provide a stationary field dielectrophoretic force, means for electrically summing two signals (page 15, line 36 to page 16, line 2) from said first frequency signal generating means and said second frequency signal generating means and applying the summed signal to the electrode array.

Independent claim 27 (as described at page 4, lines 1-10 and page 5, lines 14-15) claims a method for determining properties of a particle, including response of the particle to exposure to a chemical or physical agent, and for separating particles of more than one type, comprising steps of applying to a suspension of at least two types of particles a first signal at a first frequency and at a plurality of different phases whereby the particles experience a traveling wave dielectrophoretic force of which there is a real part which is negative and of which there is also an imaginary part, and simultaneously applying a second signal at a second frequency whereby either the real part or

the imaginary part of the traveling wave dielectrophoretic force on the particles at the first frequency is altered in magnitude, and the second frequency is selected so that the two types of particles travel in opposite directions.

As set forth at page 20, lines 6-30, by application of the inventive technique of applying a TWD force and a second signal at a frequency which modifies the TWD force, several advantageous results can be achieved, including: a) separation of cells to high specificity for identification and enumeration; b) separation of rare target cells from heterogenous samples, avoiding cell loss with a process that uses only one procedure; c) processing of samples at high cell sorting rates; d) separation of cells without the need for biochemical labeling or modification; e) isolation of viable, culturable cells with little or no biological damage; f) by increasing the travelling wave dielectrophoresis frequency window, the properties of a particle can be characterized or monitored by determining the particle's translational motion as a function of electric field frequency.

Grounds of Rejection to be Reviewed on Appeal

The grounds of rejection to be reviewed in the present appeal are –

(1) whether claims 1-6, 10, 11, 16, 17, 21 and 23 are patentable under 35 U.S.C. §102(b) over WO 97/27933 (Becker); and

(2) whether claims 1-25 and 27-31 are patentable under 35 U.S.C. §103(a) over Becker.

Argument

I. Rejection under 35 U.S.C. §102(b) of claims 1-6, 10, 11, 16, 17, 21 over WO 97/27933 (Becker).

Becker is the sole applied reference. Becker describes a method whereby a liquid containing suspended particles is caused to flow along a chamber containing a series of electrode elements. The electrodes are energized so as to impose either a stationary or a traveling wave dielectrophoretic force onto the suspended particles. Different particles are forced up to various heights above the electrode plane and into different parts of the velocity profile of the flowing liquid. As a result, different particles travel through the chamber at different

velocities, so that they exit the chamber at characteristic positions in the eluted fluid.

The claimed invention is directed to a method for separating particles in a stationary fluid. Thus, the basic physics of operation of Becker teaches nothing about applicants' claimed methodology and apparatus.

In particular, important aspects to note regarding Becker are that (1) the method depends totally on establishing a well-defined fluid flow profile above the electrodes (for example, on page 16, lines 12-13, it is stated: "The velocity of the different matter within the fluid is controlled by the velocity profile of the fluid", the method of field flow fractionation cannot work in a stationary fluid) and (2) all the particles travel along the chamber in the same direction (albeit at different velocities) determined solely by the direction of fluid flow.

Thus, Becker teaches utilizing fluid flow in the form of field flow fractionation (FFF) combined with dielectrophoresis (DEP). Field flow fractionation requires a flowing non-stationary fluid in order to separate particles in suspension. FFF works by assuming there is a non-uniform flow profile in a chamber. This is typically a

parabolic flow profile resulting from drag forces along the surface of the chamber, with maximum flow occurring in the center of the chamber (farthest from the chamber walls where friction and drag forces are their least), with flow being a minimum at the walls of the chamber (where friction and drag forces are at their maximum).

The principle of field flow fractionation is to utilize fluid flow and the fluid flow profile in conjunction with applying a secondary force perpendicular to the fluid flow. In Becker, the secondary force is dielectrophoresis. The application of the secondary force is intended to cause particles to preferentially move into different positions at differing heights within the chamber. Particles at differing heights will be positioned in a differing part of the fluid flow profile and therefore will flow at differing speeds.

Becker does not teach use of a stationary fluid. (See page 15, lines 17-21 of Becker.) Becker may choose to inject particles via the inlet port in batches or continuously. However, in order for Becker's system to work, there must be a flow of fluid through the chamber. This is secured by introducing fluid into the chamber via "ducts". There is no teaching or suggestion that fluid flow

through the chamber is other than a necessary condition for the separation of different property particles from one another. Becker teaches and relies on a velocity profile in the fluid. A velocity profile is not present in a stationary fluid.

Accordingly, the claimed invention can be contrasted to the teaching of Becker on the basis that (1) the fluid is stationary in the chamber during the process of particle separation; and (2) a secondary signal is applied in a specific way that provides novel results, namely the generation of a positive or negative cDEP force that results in extending or narrowing of the travelling wave dielectrophoresis (TWD) window. With respect to (2), this allows either the characterization of cells over a wider TWD window and thus a wider range of cellular properties, or allows the making of particles to travel at vastly different speeds or in opposite directions, that would otherwise travel in the same direction at very similar speeds. This is used, therefore, in application for separation or easy detection of a specific particle type.

Being able to complete TWD over the full dielectrophoretic spectrum or narrow the TWD window for a specific particle is significant, especially extending the

TWD window. An example is set forth in Figure 1 as contained in the Evidence Appendix hereto. Figure 1 shows that for conventional TWD (cTWD) it is only possible to characterize and differentiate cells based on size and surface morphology. It is not possible to characterize or differentiate the cells based on their cytoplasm, and nucleus properties. The invention allows completion of TWD over the full dielectrophoretic spectrum and the ability to make particles travel at vastly different speeds or in opposite directions, thereby allowing characterization of biological particles over their full ranges of cellular properties, i.e., size, surface morphology, cytoplasm and nucleus properties.

With reference to the claims, the above is implemented by applying the second signal at a second frequency which thus adds a secondary force to the particle. The net effect in this context is to either narrow or extend the TWD window, namely the frequency range, over which TWD can occur. The benefits obtained with respect to the TWD window are shown in Figures 1 , 2 and 3 as contained in the Evidence Appendix hereto. The benefits obtained upon extending the TWD window is that essentially one can characterize and/or separate particles over the full

dielectrophoretic spectrum if so desired (rather than just a narrow window of it). This is significant since cTWD (conventional non-superposition TWD) has a very limited application. The superposition TWD of the claimed invention can, therefore, achieve better selectivity and separation as compared to conventional TWD. The ability to make particles travel at vastly different speeds or in opposite directions, is either achieved by applying the second signal that results in narrowing the TWD window (by selectively applying a positive DEP force), or by applying the second signal that selectively applies a translational TWD force that results in the particles traveling at vastly different speeds or in opposite directions.

Accordingly, Becker does not teach each and every element as claimed by applicants. Thus, Becker does not anticipate the claimed invention under 35 U.S.C. §102.

II. Rejection under 35 U.S.C. 103(a) of claims 1-25 and 27-31 over WO 97/27933 (Becker).

Applicants resubmit that set forth above in Section I, and most notably that Becker does not teach a method or apparatus for separating parties in a stationary fluid. Becker teaches and requires a fluid flow with a velocity profile. A stationary fluid does not have a

velocity profile. Thus, Becker also does not suggest a stationary fluid as claimed by applicants.

Further, in the method of claim 27, separation of different particles involves different particles traveling in opposite directions to each other. The direction of travel of a particular particle type, for superposition of a set stationary field dielectrophoretic force onto a set traveling field dielectrophoretic force, is determined by the physicochemical (dielectric) properties of each particle type. Even if a traveling wave dieletrophoretic window is inherent in Becker, applicants' teach how this frequency window (meaning the range of frequencies where translational traveling motion occurs) can be extended or reduced, so as to enhance the separation of different particles.

Additionally, as a basis of obviousness, the Examiner states that the use of a third signal is asserted to being within the skill of an artisan. Applicants submit, however, that even presupposing that adding an extra signal to the electrodes is straightforward, it is not straightforward (and, therefore, unobvious in view of the lack of teaching or suggestion) as to knowing or determining what the frequency and magnitude of this third signal should be in order to change the dielectrophoretic movement of a

specific particle type in a stationary fluid. Becker does not teach this. Applicants thus submit it would not have been obvious to one of ordinary skill in the art at the time the invention was made to have varied the speed of the particles so that the particles could be separated.

Further, applicants do not agree with the Examiner's assertion that Becker teaches signals that range from 10 kHz to 10 MHz and that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a first signal of 55 kHz for TWD and a second static DEP signal at a frequency of 55 kHz, whereby the TWD window extends between 10 kHz and 18 MHz, because such is within the scope of Becker's disclosure. Applicants respectfully submit that the Examiner is confusing the concept of a TWD signal and a TWD window. The TWD signal represents the frequency of the voltage signal applied to the electrodes, whereas the TWD window represents the frequency range over which a particle can be observed to move in a stationary fluid over the electrodes. A TWD signal may be applied at 55 kHz, but whether or not the particle is induced to move depends on whether or not the TWD window includes this frequency. Applicants' invention is directed to teaching how the TWD window can be changed so

as to include (or exclude) any desired frequency. Applicants claimed invention provides for superimposing two or more different voltage signals to electrodes in order to produce particle separation in stationary fluids. Becker does not teach this.

Accordingly, Becker provides no suggestion of modifying the teaching of Becker so as to obtain applicants' claimed invention. The basic physics of operation are different than as required by applicants' claimed method and apparatus and, therefore, Becker does not teach or suggest applicants' claimed method and apparatus. Becker does not teach or suggest a method for separating particles in a stationary fluid or that a second frequency is selected so that in the separation of different particles, the two types of particles travel in opposite directions as claimed. In Becker, the method of field flow fractionation cannot work in a stationary fluid and all the particles travel along the chamber in the same direction (albeit at different velocities) determined solely by the direction of fluid flow. Accordingly, it is not possible to achieve applicants' separation method from the method of Becker.

Thus, Becker provides no suggestion of modifying the teaching of Becker so as to obtain applicants' claimed

invention. Therefore, applicants respectfully submit that the claimed invention is not rendered obvious within the meaning of 35 U.S.C. §103.

III. Applicable Law

The law supports patentability of the method and apparatus claimed.

The Court of Appeals for the Federal Circuit, in considering a rejection under 35 U.S.C. §102, stated:

> "For a prior art reference to anticipate in terms of 35 U.S.C. §102, every element of the claimed invention must be identically shown in a single reference." *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677, 7 USPQ2d 1315, 1317 (Fed. Cir. 1988). These elements must be arranged as in the claim under review, [references omitted]."

In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). Thus, anticipation under §102 is not present with regard to claims 1-6, 10, 11, 16, 17, 21 and 23.

As to the rejection under 35 U.S.C. §103, the Court of Appeals for the Federal Circuit in In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529 at 1531 (Fed. Cir. 1988), stated:

> "The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light

> of the prior art. [References omitted]. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.
>
> In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention."

It is now well settled that a rejection under 35 U.S.C. §103 must rest on a firm factual basis and that the Examiner has the initial duty of providing that factual basis. Deficiencies in the factual basis cannot be supplied by resorting to speculation or unsupported generalities. In re Warner, 379 F.2d 1011, 154 USPQ 173 (CCPA 1967) and In re Freed, 425 F.2d 785, 165 USPQ 570 (CCPA 1970).

As the Court of Appeals for the Federal Circuit stated in In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998):

> "As this court has stated, "virtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); *see also Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting

> patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *Sensonics. Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570. 38 USPQ2d 1551, 1554 (Fed. Cir. 1996).
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed."

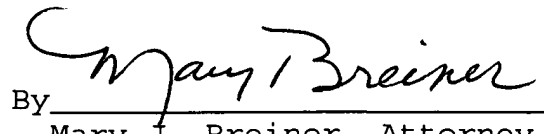
In the case at hand, there is no motivation to select the parts of the reference selected by the Examiner to meet the appealed claims for the reasons stated above.

Conclusion

It is respectfully submitted that appealed claims 1-25 and 27-31 are patentable within the meaning of 35 U.S.C. §102 and §103. Reversal of the Examiner's rejections is, therefore, respectfully urged.

Respectfully submitted,

GARY LOCK ET AL

By 

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Attachments - Claims Appendix
- Evidence Appendix
- Related Proceedings Appendix

The Appealed Claims:

1. A method for determining properties of a particle, including response of the particle to exposure to a chemical or physical agent, and for separating particles of more than one type, comprising steps of applying to a suspension of particles in a stationary fluid a first signal at a first frequency and at a plurality of different phases whereby the particles experience a traveling wave dielectrophoretic force of which there is a real part which is negative and of which there is also an imaginary part, and simultaneously applying a second signal at a second frequency whereby either the real part or the imaginary part of the traveling wave dielectrophoretic force on the particles at the first frequency is altered in magnitude.

2. A method according to Claim 1 wherein within a range of first frequencies constituting a traveling wave dielectrophoretic window, the particles experience a traveling wave dielectrophoretic force of which there is a real part which is negative and of which there is also an imaginary part, and wherein the application of the second signal causes the frequency range of the window to vary in width.

3. A method according to Claim 1 in which the frequency of the second signal is selected so that levitation height of the particles above electrodes applying the signals is varied.

4. A method according to Claim 1, 2 or 3, in which two types of particles in suspension are present, and the second frequency is selected so that speed of travel of at least one particle type is varied.

5. A method according to Claim 4 in which the second frequency is selected so that relative speed of travel of the two types of particles is increased.

6. A method according to Claim 5 in which one particle type travels and one particle type does not travel.

7. A method according to Claim 4 in which the second frequency is selected so that relative speed of travel of the two types of particles is decreased.

8. A method according to Claim 4 in which the second frequency is selected so that the two types of particles travel at the same time.

9. A method according to Claim 4 in which the second frequency is selected so that the two types of particles travel in opposite directions.

10. A method according to Claim 1, 2 or 3 in which the second signal generates a static DEP field.

11. A method according to Claim 1, 2 or 3 in which the second signal generates a second traveling wave dielectrophoretic field.

12. A method according to Claim 11 in which the first and second traveling wave fields are arranged to move the particles in different directions.

13. A method according to Claim 1 in which the second signal is applied at a frequency at which one of said real part and said imaginary part is zero and the other part is positive, so that said other part increases in value in accordance with the strength of the second signal.

14. A method according to Claim 1 in which the second signal is applied at a frequency at which one of said real part and said imaginary part of the force is substantially zero and the other part is negative, so that said other part decreases in value in accordance with the strength of the second signal.

15. A method according to Claim 1, 2 or 3 further comprising applying a third signal at a third frequency whereby either the real part or the imaginary part of the

traveling wave dielectrophoretic force on the particles is altered in magnitude.

16. A method of separating unwanted particles from body fluid particles comprising applying to a suspension of both types of particles in a stationary liquid a TWD field at a first frequency, and simultaneously applying a second electrical field at a second frequency, whereby speed or direction of travel in the TWD field of one particle type is altered.

17. A method according to Claim 16 in which an unwanted type of particles is cancer cells and the body fluid particles are blood cells.

18. A method according to Claim 16 in which the unwanted particles are bacteria and the body fluid particles are blood cells.

19. A method according to Claim 18 in which the bacteria are E-coli and the blood cells are red blood cells, the first and second frequencies being selected so that E-coli travels in the TWD field and the red blood cells do not travel.

20. A method according to Claim 18 in which the bacteria are E-coli and the blood cells are red blood cells, further comprising applying a third electrical signal at a

third frequency, the first, second and third frequencies being selected so that E-coli travels in one direction in the TWD field and the red blood cells travel in the opposite direction.

21. A method according to Claim 1 or 16 in which the second signal is selected to induce a hydrodynamic fluid movement of said suspension.

22. A method according to Claim 1 further comprising applying TWD to human blood cells comprising applying to a suspension of said cells, as first TWD, a signal at a frequency of 55 kHz and a second, static DEP signal at a frequency of 55 kHz, whereby the TWD window extends between 10 kHz and 18 MHz.

23. Apparatus for applying traveling wave dielectrophoresis comprising a dielectrophoresis cell for receiving a fixed quantity of a stationary suspension of particles in a liquid, an electrode array on a substrate forming a wall of the cell, first frequency signal generating means to provide a traveling wave dielectrophoretic force, second frequency signal generating means to provide a stationary field dielectrophoretic force, means for electrically summing two signals from said first frequency signal generating means and said second frequency

signal generating means and applying the summed signal to the electrode array.

24. Apparatus according to Claim 23 including at least a third signal generating means for applying at least a third signal to the electrodes.

25. Apparatus according to Claim 23 or 24 in which the substrate is transparent and further comprising illumination means to illuminate the substrate and viewing means to view any particles on the substrate.

27. A method for determining properties of a particle, including response of the particle to exposure to a chemical or physical agent, and for separating particles of more than one type, comprising steps of applying to a suspension of at least two types of particles a first signal at a first frequency and at a plurality of different phases whereby the particles experience a traveling wave dielectrophoretic force of which there is a real part which is negative and of which there is also an imaginary part, and simultaneously applying a second signal at a second frequency whereby either the real part or the imaginary part of the traveling wave dielectrophoretic force on the particles at the first frequency is altered in magnitude, and the second frequency

is selected so that the two types of particles travel in opposite directions.

28. A method according to Claim 27 wherein within a range of first frequencies constituting a traveling wave dielectrophoretic window, the particles experience a traveling wave dielectrophoretic force of which there is a real part which is negative and of which there is also an imaginary part, and wherein the application of the second signal causes the frequency range of the window to vary in width.

29. A method according to Claim 27 in which the second signal is applied at a frequency at which one of said real part and said imaginary part is zero and the other part is positive, so that said other part increases in value in accordance with the strength of the second signal.

30. A method according to Claim 27 in which the second signal is applied at a frequency at which one of said real part and said imaginary part of the force is substantially zero and the other part is negative, so that said other part decreases in value in accordance with the strength of the second signal.

31. A method according to Claim 27 or 28 further comprising applying a third signal at a third frequency

whereby either the real part or the imaginary part of the traveling wave dielectrophoretic force on the particles is altered in magnitude.

RELATED PROCEEDINGS APPENDIX

None.

* * * * *

Figures 1, 2 and 3 as submitted with the Response filed and entered April 13, 2006.

* * * * *

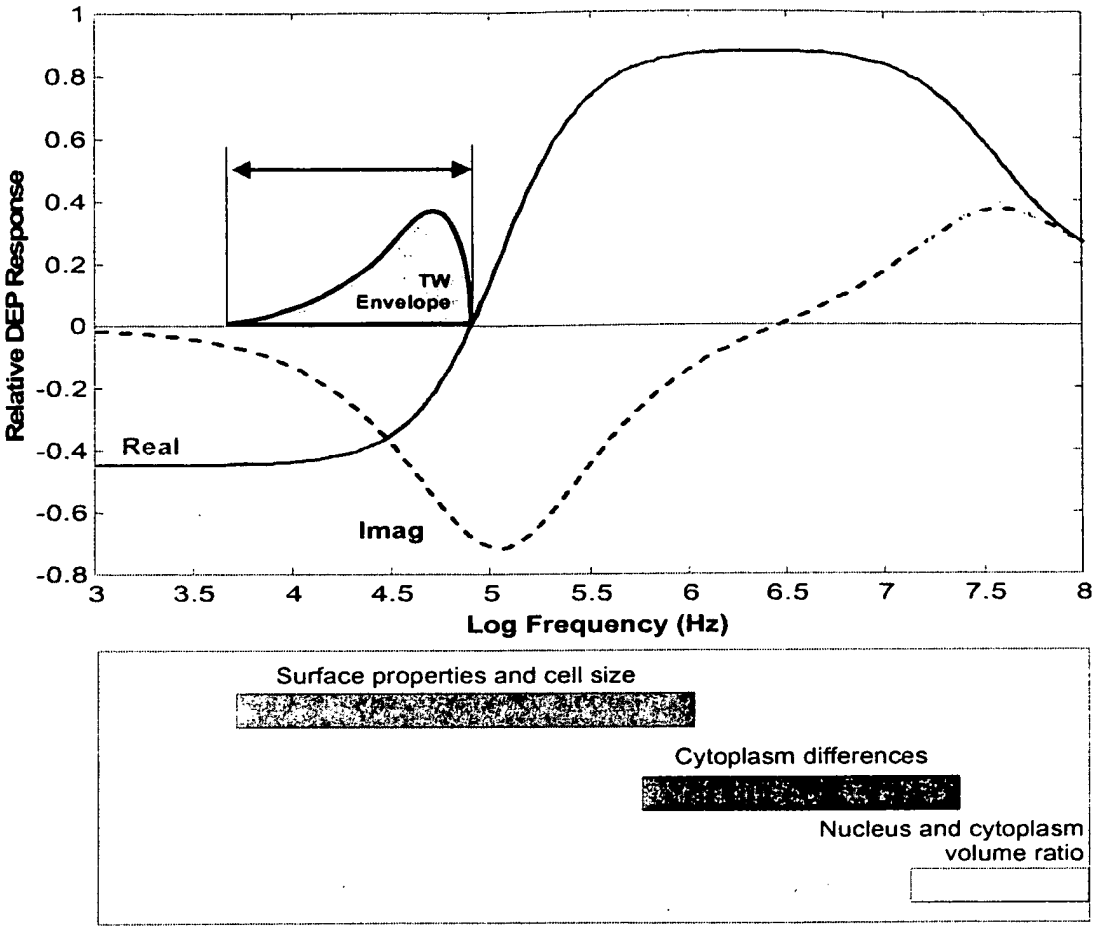

FIGURE 1

Dielectrophoretic spectrum for a human B-lymphocyte (medium 15mS/m). Relative frequency regions where differing cell properties dominate the response are shown.

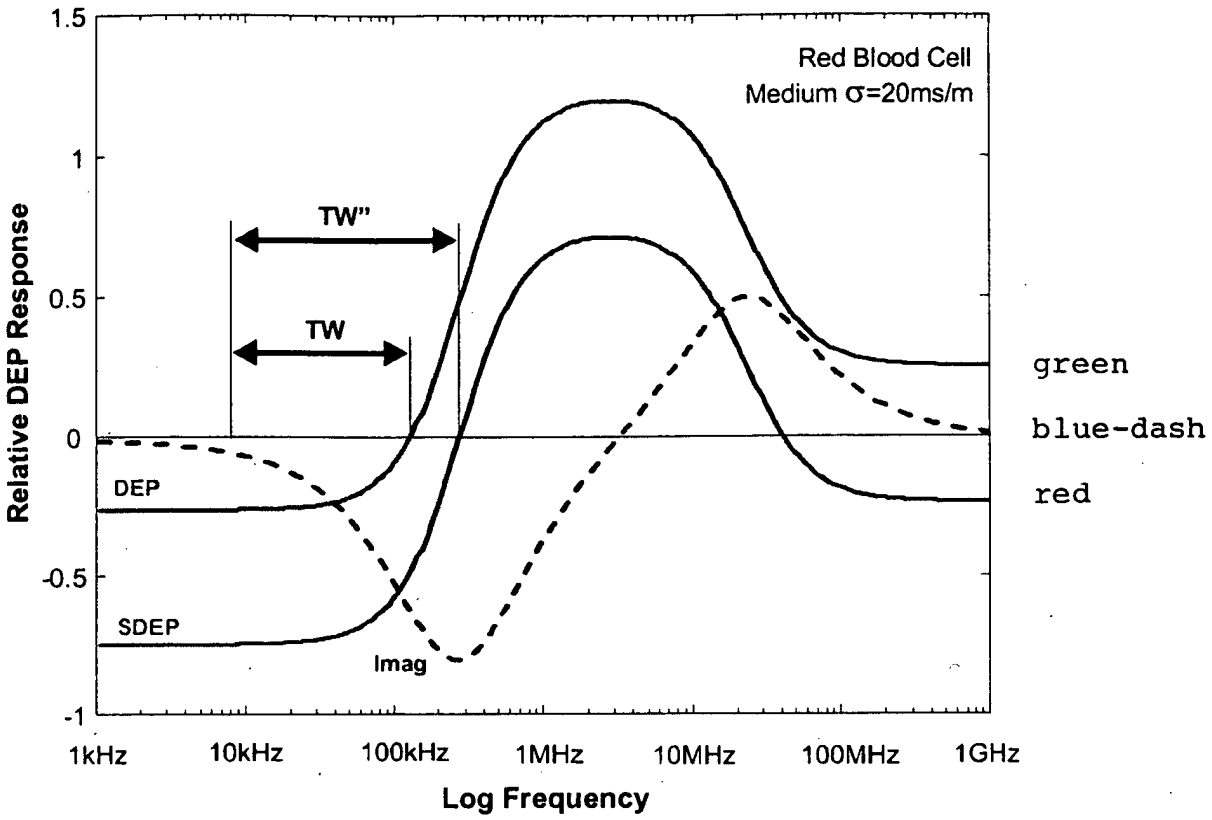

FIGURE 2

Dielectrophoretic spectrum. Blue-dash plot indicates the imaginary force $F_{DEP}(Im)$, the green plot is the real part of the DEP force $F_{DEP}(Re)$, with the red plot showing the superposition $sF_{DEP}(Re)$. The travelling wave window is seen to be extended from TW to TWD" as a result of superposition. The response shown is generated using a dielectric shell model of a red blood cell in a medium of 20mS/m and used for illustration.

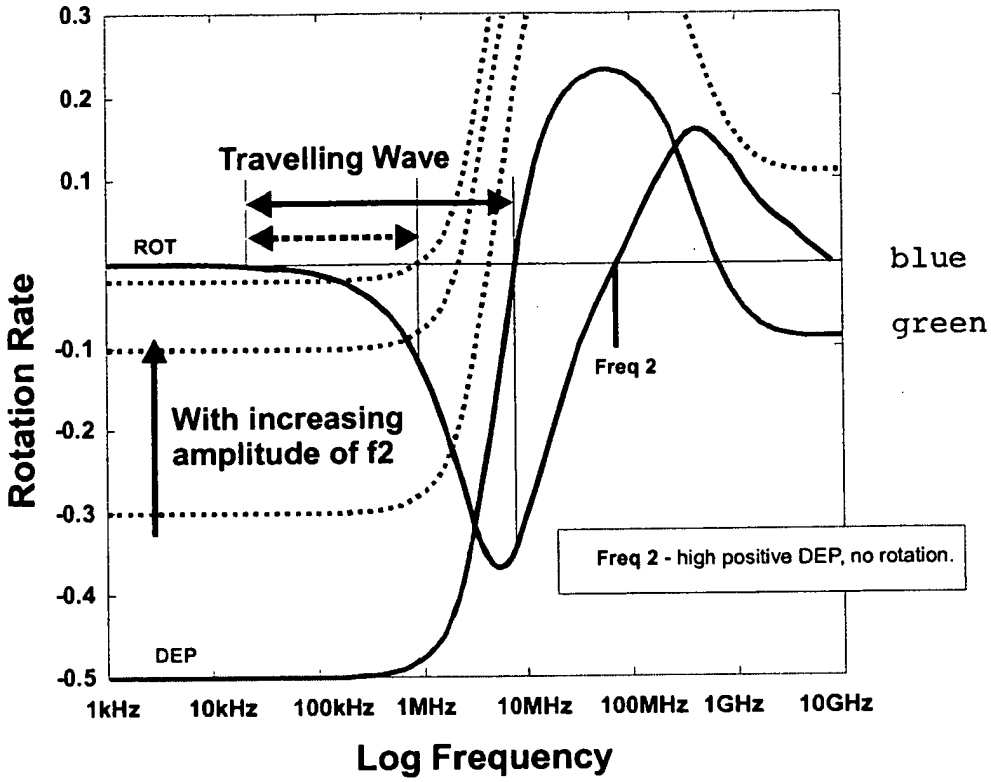

FIGURE 3

Dielectrophoretic spectrum, with superposition narrowing the TWD window.